HuGE Fact Sheet

FMR1 and the Fragile X Syndrome

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PUBLISHED: July 2001

FMR1 Gene

The fragile X mental retardation-1 (*FMR1*) gene, located at Xq27.3, codes for the mRNA-binding fragile X mental retardation protein (FMRP). FMRP is thought to shuttle select mRNAs between the cytosol and nucleus and is highly expressed in the brain, testes, ovaries, esophageal epithelium, thymus, eye, and spleen.

Prevalence Of Gene Variants

The 5' untranslated region of FMR1 contains a polymorphic CGG (cytosine-guanine-guanine) repeat that can be categorized into four classes based on the size of the repeat: common (6-40 repeats), intermediate (41-60 repeats), premutation (61-200 repeats), and full mutation (>200-230 repeats). The full mutation is the disorder-causing form of the repeat, and the premutation is the carrier form of the repeat. To date, all population-based estimates for the fragile X full mutation are derived from the screening of a target population such as a special education population. The findings are then extrapolated to the general population with the assumption that all males affected by the fragile X syndrome will be found among the targeted population. Based on this screening scheme, the prevalence of the full mutation in Caucasian populations is approximately 1 in 4,000 males to 1 in 6,000 males, with point estimates ranging from 1 in 3,717 males to 1 in 8,918 males. Little information exists for other ethnic/racial groups; however, population-based estimates in admixed, African-derived populations suggest that the prevalence of the full mutation may be 1 in 2,500 males. No study has determined the prevalence of the full mutation among females in the general population. Based on the prevalence of the full mutation in males, 1 in 8,000 females to 1 in 9,000 females in the general population may be affected by the fragile X syndrome.

For premutations (61-200 repeats), the estimates for Caucasian females range from 1 in 246 to 1 in 468 in the general population. To date, the smallest premutation to hyperexpand to the full mutation in a single generation is 59 repeats. If the threshold for premutations were lowered to 55-200 repeats, the prevalence among Caucasian females can be as high as 1 in 116, depending on the population studied. For Caucasian males, the prevalence of the premutation (61-200 repeats) is probably between 1 in 1,000 to 1 in 2,000 in the general population. No estimates exist for other racial/ethnic groups.

Disease Burden

The fragile X syndrome is the most common form of inherited mental retardation and accounts for approximately 40% of cases with X-linked mental retardation. Other characteristics of the fragile X syndrome include a wide range of cognitive, behavioral, and physical features such as variable IQ (profound to mild mental retardation), autistic-like features, hyperactivity, increased testicular volume, macrocephaly, and large ears. Females are less severely affected, presumably because of X-inactivation. In the United States, a child with the fragile X syndrome is eligible for early intervention and special education services. A screening study in a U.S. public special education population suggests that approximately 1 in 400 males receiving special education services are affected by the fragile X syndrome.

Interactions
No gene-gene or gene-environment interactions have been identified. However, such interactions are possible, because the fragile X syndrome clinical phenotype is variable and cannot be explained by the CGG repeat size or the variability of FMRP. Also, approximately 21% of premutation female carriers experience premature ovarian failure (POF: cessation of menses prior to 40 years). Full mutation female carriers do not experience POF; therefore, many researchers speculate that the large CGG repeat in the transcript is responsible for this phenotype. However, the mechanism remains to be elucidated.

Laboratory Tests
The Quality Assurance Subcommittee of the American College of Medical Genetics Laboratory Practice Committee states that the laboratory tests which effectively detect and measure the CGG repeat are more than 99% sensitive and 100% specific. These methods do not detect point mutations or deletions, which account for less than 1% of the fragile X syndrome-causing mutations. Also, intermediate alleles are considered inconclusive for carrier testing. Much research is needed to understand which intermediate alleles are susceptible to hyperexpanding to the full mutation in the next generation for the purpose of genetic counseling.

Population Testing
In 1994, a working group for the American College of Medical Genetics published guidelines for making referrals for fragile X testing. These included testing any person with unexplained mental retardation, developmental delay, or autism, especially if physical or behavioral characteristics commonly associated with the fragile X syndrome are evident. The working group also recommended carrier testing on the basis of a family history of unexplained mental retardation. The working group currently does not recommend population carrier screening. Unlike the United States, Finland and a few medical centers in Israel currently offer a fragile X test to women who are pregnant. If identified as a carrier of the fragile X premutation or full mutation, these women are offered prenatal diagnosis. Preliminary results suggest that participation in both the initial carrier testing and prenatal diagnosis is high (Finland: 85% and 100%, respectively).

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Web Sites
1. The National Fragile X Foundation
2. FRAXA Research Foundation
3. Carolina Fragile X Project
4. GeneClinics